I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as Express Airbill No. EV 543598770, in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 8-5-05 Signature: Mary Murphy (Mary Murphy)

Docket No.: VASG-P02-003 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Gill et al

Application No.: 09/487023 Group Art Unit: 1635

Filed: January 19, 2000 Examiner: McGarry, S.

For: METHOD AND COMPOSITION FOR TREATMENT OF KAPOSI'S SARCOMA

MS After Final
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 of Ruiwen Zhang

Sir:

DR. Ruiwen Zhang, M.D., Ph.D., D.A.B.T., hereby declares and states as follows:

1. I am Associate Professor of Pharmacology & Toxicology and Scientist of Comprehensive Cancer Center, Center for AIDS Research, Gene Therapy Center, Chemoprevention Center, and Center for Aging. I am also Director of Cancer Pharmacology Laboratory. I have worked on the development of cancer pharmacology and therapeutics for over 20 years. A copy of my CV is enclosed with this Declaration.

2. I have read the Office Action issued by the U.S. Patent and Trademark Office on August 5, 2004 in the above-identified patent application. I have also reviewed the references cited in the Office Action, including Uchida et al., U.S. Patent No. 6,150,092. I understand that the Examiner has rejected the pending claims as obvious in view of Uchida et al. in combination with various other references. From a scientific perspective, I do not believe that the Uchida et al. reference renders the claims of the present application obvious. Had I read the Uchida et al.

reference at the time that the present application was filed, January 19, 2000, I would not have been motivated to generate phosphorothioate (PS) modified forms of the VEGF antisense nucleic acids set forth in Uchida et al. I base this conclusion on reasons set forth below.

3. **Phosphorothioate-modified antisense probes:** First, I note that PS-modified antisense probes are designed for use in *in vivo* or cell-based applications of antisense technology. This is because PS-modified nucleic acids have improved resistance to nucleases found in cells. One would have no reason to make a PS-modified form of an antisense nucleic acid unless one intended to use the antisense construct to affect gene expression in cells. Therefore, a demonstration that an unmodified antisense probe is effective in a cell-free assay would not necessarily provoke one to make and test the PS-modified form in a cell-based assay. This is particularly true where, as with Uchida et al., there is a poor correlation between the results seen in the cell-free and cell-based assays.

4. **Cell-free Assays:** Uchida et al. describe experiments testing antisense probes for their effects on VEGF expression. The majority of the data presented by Uchida et al. were based on cell-free assays employing unmodified DNA antisense probes at a concentration of 0.4 micromolar (see, Tables 1-8 of Uchida et al. and col. 20, line 3). Tables 1 and 2 in particular show that dozens of unmodified antisense probes were effective in decreasing VEGF expression in the cell-free assay. In many instances VEGF expression was decreased by greater than 90%.

5. **Cell-based Assays:** Uchida et al. selected six probes that were highly effective in the cell-free assays and tested PS-modified forms of these probes in a cell-based assay. The effects of these probes on VEGF expression in cells are shown in Table 9. The amount of VEGF expression observed by Uchida et al. in the presence of the PS-modified probes was high, ranging from 54% to 70% of normal (59% to 82% when corrected for the baseline inhibition seen in the controls).

The cell-based assays of Uchida et al. were performed with PS-modified probes at the high concentration of 20 micromolar (Col. 25, line 30). The cell-free assays in Tables 1 and 2 were performed at a concentration of 0.4 micromolar. At a concentration of 20 micromolar, it is often difficult to discern whether an effect on gene expression is due to a specific antisense effect

or a generalized effect on cellular processes. Given the high probe concentration and the small observed effect on VEGF expression in the cell-based assays, I conclude that the antisense probes identified by Uchida et al. are not effective for inhibiting VEGF expression in cells. These data would not have motivated me to modify and test other probes disclosed by Uchida et al. for use in cells.

6. **A Comparison of the Cell-free and Cell-based Assays:** There is a poor correlation between the effectiveness of the unmodified probes in the cell-free assays and the PS-modified probes in the cell-based assays. For example, the unmodified probe A311 (SEQ ID NO:51) inhibited 96% of VEGF expression in the cell-free assay, but the PS-modified form of A311 inhibited only 22% to 28% of VEGF expression in the cell-based assay (at a 50-fold higher concentration). Of six probes that were effective in cell-free assays, all six showed only mild effect on VEGF expression in the cell-based assay. I conclude that there is no reason to expect that any of the probes that Uchida et al. identified in the cell-free assay would be likely to be effective as PS-modified forms.

7. I further state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 27, 2005

Signed: _____

Dr. Ruiwen Zhang, M.D., Ph.D., D.A.B.T.

STANARDIZED CURRICULUM VITAE
UNIVERSITY OF ALABAMA AT BIRMINGHAM
SCHOOL OF MEDICINE FACULTY

DATE: May 4, 2005

PERSONAL INFORMATION

Name:	**Ruiwen Zhang, M.D., Ph.D., D.A.B.T.**
Citizenship:	The United States of America
Foreign Language(s):	Chinese; Japanese (reading)
Home Address:	4744 Outlook Way Marietta, GA 30066
Telephone and FAX:	(770) 578-6965

RANK/TITLE

Associate Professor
(Professor, Effective October 1, 2005)

Department:	Pharmacology and Toxicology
Division:	Clinical Pharmacology
Business Address:	The University of Alabama at Birmingham Department of Pharmacology and Toxicology VH 113, Box 600 1670 University Blvd. Birmingham, AL 35294-0019
Business Telephone:	(205) 934-8558
Business FAX:	(205) 975-9330
Business E-Mail:	ruiwen.zhang@ccc.uab.edu

PROFESSIONAL CONSULATSHIPS:

2003-2008	US FDA Consultant, Clinical Chemistry and Clinical Toxicology Devices Panel, Medical Devices Advisory Committee, Center for Devices and Radiological Health, FDA
1996-1999	Senior Advisor to the Director General -- National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Health, P.R. China

EDUCATION

Institution	Degree	Year
Shanghai Medical University (SMU)	**M.D. (with highest honor)**	1983
Shanghai Medical University (SMU)	**Ph.D.** (Toxicology and Occupational Epidemiology)	1988

BOARD CERTIFICATION

1999	**Diplomate, American Board of Toxicology (D.A.B.T.)**
2004	**Recertification of D.A.B.T.**

POSTDOCTORAL TRAINING

1989-1992	**Post-Doctoral Fellow/Clinical Pharmacology Fellow**, University of Alabama at Birmingham (UAB).

ACADEMIC APPOINTMENTS (in reverse chronological order)

Year	Rank/Title	Institution
2005-Present	Professor (tenured)	Clinical Pharmacology, Pharmacology and Toxicology, UAB
2002-Present	Scientist	Center for Aging, UAB
2001-Present	Scientist	Gene Therapy Center, UAB
1999-2005	Associate Professor (tenured)	Clinical Pharmacology, Pharmacology and Toxicology, UAB
1999-Present	Director	Cancer Pharmacology Laboratory, CCC, UAB
1999-Present	Scientist	UAB Comprehensive Cancer Center
1999-Present	Scientist	UAB Center for AIDS Research
1998-Present	Member	UAB Chemoprevention Center
1995-Present	Faculty Member	MD/PhD Program, UAB School of Medicine
1992-Present	Graduate Faculty	UAB Graduate School

Year	Rank/Title	Institution
1994-1999	Assistant Professor (tenure-track)	Clinical Pharmacology, Pharmacology and Toxicology, UAB
1992-1999	Associate Scientist	UAB Comprehensive Cancer Center
1992-1999	Associate Scientist	UAB Center for AIDS Research
1992-1994	Res. Asst. Professor	Clinical Pharmacology, UAB
1989-1992	Clinical Pharmacology Fellow/ UAB Research Associate	
1988-1991	Assistant Professor	Toxicology and Occupational Medicine, SMU
1983-1988	Research/Teaching Associate	Toxicology and Occupational Medicine, SMU
1981-1983	Intern and Resident	SMU Teaching Hospitals

AWARDS AND HONORS

- Distinguished Medical Student (SMU, 1979, 1980, 1981, 1982, 1983)
- Outstanding Student of Shanghai (Shanghai, 1983)
- Rong-Lin Medical Prize (Distinguished Medical Graduate, First Place, the highest honor for MD, SMU, 1983)
- Natural Science Research Grant -- *Toxicology of Formaldehyde* (China, 1986-88)
- Excellent Publications Awards (2) --*Toxicology of chlordimeform* (China, 1987)
- Excellent Publications Award -- *Toxicology of Formaldehyde* (China, 1990)
- National Research Awards --*Toxicology and Occupational Health of Formaldehyde* (Ministry of Labor, China, 1992)
- Member, Board of Directors, Association of Retard Citizens of Jefferson Co.(1994-97)
- International Leadership -- American Biographic Institute, 1994
- Board Member, Research -- American Biographic Institute, 1994-
- Senior Advisor to the Director General -- National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Health, P.R. China, 1996-1999
- Adjunct Professor -- National Institute for the Control of Pharmaceutical and Biological Products, 1996-1999
- Visiting Professor -- National Academy of Medical Sciences, Beijing, China (Supported by a grant from China National Science Foundation), 1997-
- Faculty Sponsor for ASCPT Presidential Trainee Award (Dr. Xiao-fei Zeng), 1998
- Visiting Scientist, National Clinical Pharmacology Program, Baylor College of Medicine, Houston, TX, 1999
- Faculty Sponsor for ASCPT Presidential Trainee Award (Dr. Hui Wang), 2000

- Faculty Sponsor for 2000 International Society of Predictive Oncology (ISPO) Travel Award (Dr. Hui Wang), 2000
- Faculty Sponsor for 2000 UAB Medical Student Research Competition and National Competition Travel Award (Gautam Prasad, First Place), 2000
- Faculty Sponsor for 2001 National Medical Student Research Forum (Gautam Prasad, Best paper on Oncology), 2001
- Faculty Sponsor for 2003 Graduate Student Travel Award (Zhuo Zhang), UAB
- Faculty Sponsor for 2004 Outstanding Graduate Student (Zhuo Zhang), UAB
- Faculty Sponsor for 2004 Outstanding International Student (Academic Excellence) (Zhuo Zhang), UAB
- Faculty Sponsor for DoD Prostate Cancer Research Program/Post-Doctoral Fellowship (Zhuo Zhang), UAB (2004-2006)
- Adjunct Professor – Nanjing Medical University, 2005-present

PROFESSIONAL SOCIETIES/MEMBERSHIPS

- American Association for Cancer Research (AACR)
- American Society for Biochemistry and Molecular Biology (ASBMB)
- American Society for Clinical Pharmacology and Therapeutics (ASCPT)
- American Association of Pharmaceutical Scientists (AAPS)
- American College of Toxicology (ACT)
- Fellow, Molecular Medicine Society
- American Society for Microbiology (ASM)
- American Chemical Society (ACS)
- Drug Information Association (DIA)
- American Association for the Advancement of Science (AAAS)
- International Society for Nucleosides, Nucleotides, and Nucleic Acids (IS3NA)
- Society of Chinese Bioscientists in America (SCBA)

COUNCILS AND COMMITTEES

(Federal/National/International Review Panel/Study Section; Partial List; After 2000)

2000	Reviewer, DOD Research Programs
2000	Reviewer and Study Section Member, Michigan Life Science Corridor
2002	DOD Breast Cancer Research Program, Panel Member (Molecular Biology and Genetics-4)
2002-date	NIH Study Section ZRG1 SSS-1 10B (Diagnosis and Treatment of Cancer)
2003	DOD Breast Cancer Research Program, Panel Member (Pathobiology 5)
2003	DOD Breast Cancer Research Program, Panel Member (Ad hoc panel-2)
2003	Reviewer, Cancer Research UK
2003-2008	US FDA Consultant, Clinical Chemistry and Clinical Toxicology Devices Panel, Medical Devices Advisory Committee, Center for Devices and Radiological Health, FDA

2004	DOD Prostate Cancer Research Program, Panel Member (Cell biology 3)
2004	DOD Breast Cancer Research Program, Panel Member (Molecular Biology and Genetics-3,)
2004	DOD Breast Cancer Research Program, Panel Member (Pathobiology 5)
2004	Reviewer, Florida Department of Health Biomedical Research Program
2004	Study Section, Center for Disease Control and Prevention (CDC) Peer Review (R01 Panel 2)
2004	Reviewer, US Civilian Research Foundation
2004-date	NIH Study Section BMCT (Basic Mechanisms for Cancer Therapeutics)
2004	NIOSH Study Section/Big NORA (intramural programs; National Occupational Research Agenda)
2005	DOD Breast Cancer Research Program (2004-Concept Award)
2005	DOD Prostate Cancer Research Program, Panel Member (Cell Biology 2)
2005	DOD Prostate Cancer Research Program, Panel Member (Clinical and Experimental Therapeutics 1)
2005	Reviewer, James and Esther King Biomedical Research Program, Florida
2005	NIH/NCI P01 Program Study Section, Radiation Biology
2005	Reviewer, CDC Foundation Peer Review
2005	Reviewer, International Science and Technology Center, Science and Technology Center in Ukraine
2005	Reviewer, Wellcome Trust, UK
2005	DOD Breast Cancer Research Program, Panel Member (Pathobiology 5)
2005	DOD Anti-Radiation Drug Development Program, Panel Member
2005	Reviewer, Catalan Agency for Health Technology Assessment and Research (CAHTA), Cancer Research Program, Spain

UNIVERSITY COMMITTEES

1994-	Faculty Member, MD/PhD Program, School of Medicine
1995-	Clinical Study Review Committee, Comprehensive Cancer Center
1996-	Cancer Prevention Working Group, Comprehensive Cancer Center
1996-	Lung Cancer Working Group, Comprehensive Cancer Center
1996-	Faculty Member, Clinical Investigators Training Program, School of Medicine
1997-	Brain Tumor Working Group, Comprehensive Cancer Center
1998-	Member, Chemoprevention Center
1999	Judge, UAB Medical Student Research
2000	Reviewer, American Cancer Society Institutional Grants
2000	Reviewer, Junior Faculty Development Grants
2002-2003	Member, Basic Science Advisory Committee (BSAC), UAB SOM
2002	Judge, Comprehensive Cancer Center Research Competition.
2003	Reviewer, American Cancer Society Institutional Grants
2004	Reviewer, American Cancer Society Institutional Grants
2005	Reviewer, Junior Faculty Development Grants

EDITORIAL BOARD MEMBERSHIPS

2000-date Editorial Advisory Board, ***Current Cancer Drug Targets***
2000 Executive Guest Editor, ***Current Cancer Drug Targets***
2002-date Editorial Advisory Board, ***Letters in Drug Design and Discovery***
2003-date Editorial Advisory Board, ***Medicinal Chemistry Reviews -Online***
2003-date Editorial Advisory Board, ***Drug Design Reviews -Online***
2003-date Editorial Committee for Pharmacology, ***Foxwell & Davies***
2004-date Editorial Board, ***Medicinal Chemistry***
2004-date Associate Editor, ***Therapeutics and Clinical Risk Management***
2004-date Editorial Board, ***Current Medicinal Chemistry***
2004-date Editorial Board, ***Journal of Biological Sciences***
2004-2005 Executive Guest Editor, ***Current Cancer Drug Targets***
2005-date Editorial Board, ***Recent Patent Reviews on Anti -Cancer Drug Discovery***
2005-date Editorial Board, ***Current Medicinal Chemistry-Anti-Cancer Agents***

REVIEWER FOR SCIENTIFIC JOURNALS

Biochemical Pharmacology
Biological Procedure-online
Bioorganic and Medicinal Chemistry
Cancer
Cancer Epidemiology, Biomarkers and Prevention
Cancer Research
Clinical Cancer Research
Clinical Pharmacology and Therapeutics
Current Pharmaceutical Design
Expert Opinion on Therapeutic Patents
Expert Opinion on Therapeutics
Gynecological Oncology
Hepatology
Journal of Biomolecular Screening
Journal of Clinical Oncology
Journal of Liposome Research
Journal of Pharmaceutical Science
Journal of Pharmacology and Experimental Therapeutics
Molecular Cancer Therapeutics
Molecular Medicine
Neoplasia
Oligonucleotides
Oncogene
Pharmaceutical Development and Technology
Southern Medical Journal

MAJOR RESEARCH INTERESTS

- Molecular cancer biology and molecular cancer therapeutics

- Molecular, biochemical, and clinical pharmacology and experimental therapeutics
- Gene regulation and silencing
- Biotechnology and biopharmaceuticals

In my laboratory, there are three major research projects: 1) cancer chemotherapeutics; 2) oligonucleotide-based gene expression modulators; and 3) chemopreventive agents.

1. BIOCHEMICAL AND MOLECULAR PHARMACOLOGY OF ANTI-CANCER THERAPEUTIC AGENTS

In my laboratory, major efforts in this area are devoted to development of novel small molecular therapeutic agents with defined targets. This project includes the following research areas:

1) p53 and MDM2 as a target for cancer therapy;
2) Apoptosis as a mechanism for cancer chemotherapy;
3) Natural product protein kinase C modulators;
4) Natural product topoisomerase I inhibitors;
5) Biological and chemical modulators of chemotherapy and radiation therapy.

In addition, as a key investigator of the Cancer Pharmacology Program and Director of Cancer Pharmacology Laboratory in the UAB Comprehensive Cancer Center, I have been intensively involved in clinical trials of anticancer agents including taxol, taxotere, cisplatin, carboplatin topotecan, 9-AC, gemcitabine, and fluoropyrimidines. We are also one of the major laboratories that have NCI contracts to carry out pre-clinical studies of novel therapeutic agents for cancer and AIDS.

2. OLIGONUCLEOTIDE THERAPEUTICS (ANTISENSE, RNAi and CpG IMMUNOMODULATORS)

The use of antisense oligonucleotides targeted to mRNA represents a specific, genetic-based therapy. Antisense oligonucleotides have been suggested to have a potential role in the treatment of cancer, AIDS, hepatitis, and other diseases. My research has been centered around oligonucleotide phosphorothioates and their modified analogs as gene expression modulators in the treatment of HIV/AIDS and cancers. Three oligonucleotides studied in my laboratory have entered clinical trials. We will continue to investigate in the following areas:

1) Novel targets for oligonucleotide-based therapy;
2) Pharmacokinetics and pharmacodynamics of oligonucleotide therapeutics;
3) Mechanisms of action and toxicity;
4) Clinical pharmacokinetics and clinical trials;
5) Novel means for drug delivery of oligonucleotides; and
6) Combination therapy with oligonucleotide therapeutics (chemosensitization and radiosenstization).

Current targets for oligonucleotide-based therapy in my laboratory include HIV, protein kinase A, MDM2, Bcl2, VEGF, TGF-β, ICAM-1, survivin, beta-catenin, and p53. More recently, we have been developing immuno-stimulatory oligonucleotides (IMOs) as therapeutic agents for cancer, allergy, and infectious diseases.

3. PRECLINICAL AND CLINICAL STUDIES OF CANCER CHEMOPREVENTIVE AGENTS

In my laboratory, major efforts in this area are devoted to pre-clinical and clinical development of chemopreventive agents. This project includes the following research areas:

1) In vitro/in vivo correlation of anti-proliferative effects;
2) DNA damage and DNA repair;
3) In vivo pharmacokinetics and metabolism of novel chemopreventive agents; and
4) Apoptosis and oncogene as targets for cancer chemoprevention.

In addition, I have been involved in several clinical trials of cancer prevention in the UAB Comprehensive Cancer Center as a key investigator in clinical pharmacology and toxicology, including sulindac, 9-Cis RA, I-3-C, and celecoxib.

TEACHING EXPERIENCE

1992- Department of Pharmacology and Toxicology, UAB

Lecture: *Pharmacogenetics* (Graduate Pharm I)
Clinical Pharmacology (Clinical Investigator Training Course)
Antisense Gene Therapy (Pathology Graduate 790)
Cancer Chemotherapy (Medical/Dental/Optometry Pharmacology; Graduate Pharmacology PHR705, 706)
Antifungal Chemotherapy (Medical/Dental/Optometry)
Regulatory Toxicology (Graduate Toxicology TOX 712)
Good Laboratory Practice (Graduate Toxicology TOX 712)
Clinical Toxicology (Medical Pharmacology)
Drug Design (IBS)

Course Director: *Modern Drug Design and Development* (PHR725)
Lectures (8) for this Course: *Introduction to Drug Design and Development; Rational Drug Design; In vitro Pharmacology; In vivo Pharmacology and Disease Models; New Approaches to Non-Clinical Biodisposition Studies; GLP/GMP/GCP; Clinical Pharmacology in Drug Development; Contract Research.*

1990- Division of Clinical Pharmacology, UAB
Laboratory/experimental training for graduate and medical students, visiting scholars, and postdoctoral fellows

1985-89 Shanghai Medical University, Schools of Medicine and Public Health
Coursemaster: *Toxicology*
Occupational Medicine
Lecture: *Biostatistics*
Molecular Epidemiology

Mentor/Advisor to Trainees

Post-Doctoral Fellows/Visiting Scientists

X. Cheng, BS Visiting Scientist (1992-94)

	Current Status: Post –Doc, UAB
H. Zhao, MD	Post-doctoral Fellow (1993-95) Current Status: Sr. Scientist, CDC, Atlanta, GA
X. Zhang, MD, PhD	Post-doctoral Fellow (1994-95) Current Status: Research Associate, Mount Saina Medical Center, NY
Q. Cai, MD, PhD	Post-doctoral Fellow (1995-97) Current Status: Assistant Professor, Vanderbilt University
M. Liao, MD, MSc	Sr. Visiting Scientist (1996) Current Status: Professor and Director, Beijing Institute of Pharmacology and Toxicology, China
Y. Lu, PhD	Sr. Visiting Professor (1996-97) Current Status: Professor, Beijing University of Chinese Traditional Medicine, China
X. Zeng, PhD	Post-doctoral Fellow (1997-98) Current Status: Professor and Dean, School of Environment and Life Science, Liaoning University, China; Deputy Director, Department of Public Health, Liaoning Province, China
P. Oliver, PhD	Post-doctoral Research Associate (1998-2000) Current Status: Research Associate, UAB Comprehensive Cancer Center
H. Wang, MD, PhD	Post-doctoral Fellow/Research Associate (1998-2000) Current Status: Assistant Professor, UAB Pharmacology and Toxicology and Comprehensive Cancer Center
Z. Wang, PhD	Post-doctoral Fellow (2000-2001) Current Status: Professor and Dean, School of Natural Sciences, Hebei Agriculture University, China
S. Wang, MD	Visiting Scholar (2000-2001) Current Status: Adjunct Assistant Professor, HHMI/UAB
P. Liang, MD	Visiting Scholar (2000) Current Status: Research Assistant, UAB Center for Aging
X. Yang, MD	Post-doctoral Fellow (2000-2001) Current Status: Professor, Hunan Medical University, China
Z. Shi, MD	Post-doctoral Fellow (2001-2002)

Current Status: Post-doctoral Fellow, UAB Department of Pathology

J. Hang, MD Post-doctoral Fellow (2001)
Current Status: Sr. Scientist, Peking Union Medical College/Cancer Hospital, Beijing, China

L. Lin, MSc Sr. Visiting Scientist (2001-2002)
Current Status: Sr. Scientist, National Center for Biotechnology and Bioengineering, Beijing, China

M. Li, MD Post-doctoral Fellow (2001-2003)
Current Status: Research Associate, UAB Pharmacology and Toxicology

Jian-He Wu, MD Post-doctoral Fellow (2004-)

W. Wang, MD, MSc Post-doctoral Fellow/Research Associate (2004-)

D. Cheng, MD, PhD Post-doctoral Fellow (2004-)

Mentor/Committee Member for Graduate/Medical Students

G. Prasad, BS MD- PhD Student (Mentor/Committee Chair, 2000-2004)
Current Status: M.D. student, UAB Medical School/UCSF Radiation Oncology fellowship

Z. Zhang, MD PhD Student, Pharmacology (Mentor/Committee Chair, 2000-2004)
Current Status: Post-doctoral fellow, UAB Medical School

V. Schachinger MS Student, Pharmaceutical Sciences, University of Vienna, Austria (Mentor/Thesis Research, 2002-2003)

M. Haslinger MS Student, Pharmaceutical Sciences, University of Vienna, Austria (Mentor/Thesis Research, 2002-2003)

C. Blauquiceh, BS PhD Student, Pharmacology (laboratory rotation, 1999; Committee Member, 2002-2005)

E. Rayburn, BS Ph.D. Student, Toxicology (Mentor/Committee Chair, 2003-)

R. H. Graves, BS Ph.D. Student, Chemistry (Committee Member, 2003-)

K. A. Delaine, BS Ph.D. Student, Toxicology (Mentor/Committee Chair, 2003-)

A. P. Cunningham, BS M.S. Student, Biology (Committee Member, 2004-)

X. Zhang, BS Ph.D. Student, Environmental Health Sciences (Committee Member, 2003-)

Chanel Douglas, BS	Ph.D. Student, Microbiology (Committee Member, 2005-)

Laboratory Training for Graduate/Medical Students

R. Guttman, BS	Graduate Student, Pharmacology (laboratory rotation, 1991-93)
S. Wiggins, BS	Medical Student (summer research, 1992)
N. Zou, BS, MSc	Graduate Student, Pharmacology (laboratory rotation, 1992)
J. Adams, BS	Medical Student (laboratory rotation, 1994)
T. Williams, BS	Graduate School Summer Internship (1996)
R. Mathew, BS	MPH Graduate Student Research Assistant (1997-1999)
Long P. Le, BS	M.D.- Ph.D. Student (laboratory rotation, 1999-2000)
P. Mookherjee, MS	Graduate Student, Pharmacology (laboratory rotation, 1999)
Y. K. Holt, BS	Graduate Student Summer Internship (1999)
X. Li, BS	Ph.D. Student, Pharmacology (laboratory rotation, 1999)
H. Someya, BS	Ph.D. Student, Pharmacology (laboratory rotation, 2000)
T. D'Alessandro, BS	Ph.D. Student, Pharmacology (laboratory rotation, 2000)
P. Huang, BS	Ph.D. Student, Pharmacology (laboratory rotation, 2002-2003)
M. Sun, BS	Ph.D. Student, IBS (Dissertation Research 2002-2003)
A. Lee, BS	Ph.D. Student, Toxicology (laboratory rotation, 2003)
J. Cramton, BS	Ph.D. Student, Toxicology (laboratory rotation, 2003)
Y. Wang, BS, MS	Ph.D. Student, IBS (laboratory rotation, 2003-2004)
Ashish P. Mogal, BS	Ph.D. Student, IBS (laboratory rotation, 2004)
L. Zhai, BS	Ph.D. Student, IBS (laboratory rotation, 2004-2005)
E. Bashari, BS	Ph.D. Student, IBS (laboratory rotation, 2005)

Work-Study Students/Student Assistants

J. Miller, BS	Work-Study (1989-90)
M. Lusco, BS	Student Assistant (1990-93)
S. Webb, BS	Student Assistant (1992-93)
C. Diasio, BS	Student Assistant (1992-94)
T. Thomas	Work-Study (1992-93)
S. Howland	Work-Study (1992-93)
J. Young	Work-Study (1993-94)
A. Chaves	Work-Study (1993-95)
D. Fletcher, BS	Work-Study (1993-96)
C. Shoemaker	Student Assistant (1994-95)
L. High, BS	Work Study/Student Assistant (1994-97)
S. Avery	Student Assistant (1999)
K. Wang	Student Assistant (2002-2004)
A. Mel	Student Assistant (2002-2003)
B. Ku	Student Assistant (2003)
A. Peyyala, BS	Student Assistant (2003-2004)
K.G.Chaitanya, BS	Student Assistant (2003-2004)

MAJOR LECTURES AND VISITING PROFESSORSHIPS

2005 **Shanghai Jiao Tong University**: Drug development: Move forward by failing early, fast, and often. May

2005 **Nanjing Medical University**: P53-dependent and independent activities of MDM2: Implication in Cancer development, Prevention and Treatment. April

2005 **2005 Bio-forum, Shanghai**: Accelerating Drug development by novel approaches to pharmacology and toxicology evaluations. April

2005 **University of California, Los Angles**: Genistein, a soy product, down-regulates the MDM2 oncogene, a previously unrecognized mechanism of action. April

2005 **Emory University, Winship Cancer Institute**: MDM2; Big brother of p53 and other molecules. April

2005 **Chinese Academy of Medical Sciences, Cancer Institute**: Novel oligonucleotide therapeutics. March

2005 **Chinese Academy of Sciences, Shanghai Institute for Nutritional Sciences**: Nutrition-gene interaction. March

2004 **Nantong University, China:** RNA Silencing—Research and Development. December

2004 **Chinese Academy of Sciences/Institute of Nutritional Sciences:** Advances in gene silencing. December

2004 **NIH 7th Symposium on Oligonucleotide Therapeutics**: Novel mixed-backbone oligonucleotides in cancer therapy: Monotherapy and combination therapy with chemotherapeutic agents, radiation, and monoclonal antibodies. December

2004 **Peking Union Medical College and Chinese Academy of Medical Sciences/Cancer Institute/Cancer Hospital:** Advances in experimental therapeutics for human cancers. August

2004 **UAB Center for Aging and Birmingham/Atlanta VA Geriatric Research, Education and Clinical Center**: Oligonucleotide Therapeutics. February

2003 **Peking Union Medical College and Chinese Academy of Medical Sciences/Cancer Institute/Cancer Hospital:** cAMP-dependent Protein Kinase (PKA) and Cancer. October

2003 **Dalian University of Technology:** Nucleic Acids Therapeutics. October

2003 **NYU Medical Center:** RNA Silencing: Research and Development. August

2003 **Texas Tech University School of Pharmacy**: Antisense Oligonucleotide Therapeutics: Are We There Yet? March

2003 **UAB Department of Medicine/Division of Hematology and Oncology**: Chemosensitization and Radiosensitization by Antisense Oligonucleotides. March

2002 **NIH 6th Symposium on Oligonucleotide Therapeutics**: Chemosensitization and Radiosensitization by Antisense Oligonucleotides. December

2002 **NIH**: p53-Dependent and p53-independent activities of MDM2: Antisense approach. September

2001 **NIH**: Antisense Anti-MDM2 Oligonucleotide Therapeutics as a New Approach to Human Cancer Therapy: In vitro and In vitro Studies. April

2001 **UAB Department of Medicine/Division of Hematology and Oncology:** Antisense Anticancer Therapeutics. April

2001 **UAB Comprehensive Cancer Center**: Translational Research/Cancer Pharmacology. June

2001 **UAB Gene Therapy Center**: Antisense Gene Therapy, Birmingham, AL, February.

2000 **Chinese Academy of Medical Sciences**: PKA as a Biomarker for Cancer Early Detection. Beijing, China, December.

2000 **The Post-Genome Biotechnology Conference**, Hangzhou, China: Antisense Technology, October.

2000 **The fourth Life Sciences Symposium**, Beijing, China: Inhibiting MDM2 expression as a novel approach to human cancer therapy, August.

2000 **The Annual Meeting of Southeastern Pharmacology Society**, Jackson, MS: MDM2 as a novel target for human cancer therapy, August.

2000 **The Fifth World Congress on Advances in Oncology**: Protein Kinase A as a new target for cancer therapy, October.

1999 **Baylor College of Medicine**: Antisense Oligonucleotide Therapeutics: Preclinical and Clinical Pharmacology, April.

1999 **University of Mississippi**: Antisense Technology: Rationale, Design, and Evaluation. March.

1999 **Brown University**: Antisense Gene Therapy, January.

1998 **The Annual Meeting of Southeastern Pharmacology Society**: Oligonucleotide Therapeutics; Preclinical and Clinical Pharmacology. Sept.

1998 **The Third World Congress on Advances in Oncology**: MDM2 as a new target for cancer therapy, Greece, October.

1998 **The 6th Pacific Rim Biotechnology Conference and Bioexpo 98**: Antisense Oligonucleotide Therapeutics: Promises and Pitfalls, June.

1997 **Chinese Academy of Medical Sciences**: Visiting Professor Lecture--Pharmacogenetics: Principles and Applications, Beijing, China, October

1997 **Shanghai Medical University**: Principles and Practice of Modern Drug Development, Shanghai, China, October.

1997 **The First International Symposium on Gene Therapy**: Antisense Oligonucleotides as Gene Expression Modulators, Beijing, China, July.

1997 **Chinese Academy of Medical Sciences**: Antisense Oligonucleotides as Gene Expression Modulators: New Generation of Therapeutics? Beijing, China, July.

1997 **NIH**: Preclinical and Clinical Pharmacology of Oligonucleotide Therapeutics. NIH, Bethesda, MD, Jan.

1996 **UAB Comprehensive Cancer Center**: In Vitro an in Vivo Anti-tumor Activity of Antisense Oligonucleotides Targeted at Protein Kinase A. Oct.

1996 **Sino-US Workshop**: Organizing Committee Member and Invited Speaker; A 3-day workshop, **Advances in pharmaceuticals: Academic, industrial, and regulatory aspects**, Beijing, China, July 7-9. Lectures included:
1) New Drug Development in USA;
2) New Drug approval: Preclinical Pharmacology and Toxicology;
3) Contract Research;
4) New Biotechnology in Drug Development;
5) Latest Development in Clinical Trials; and
6) Gene Therapy.

1996 Invited Speaker: **Sino-US workshop, Advances in Clinical Trials**. Shanghai Institute of Planned Parenthood Research, Shanghai, China; September 26-29. Presentations included:

1) GLP in Preclinical Pharmacology and Toxicology;
2) Contract Research Organization; and
3) Comparison of Drug Regulatory System in USA and China.

1995 **International Conference "Therapeutic Oligonucleotides From Cell To Man"**: Comparative Pharmacokinetics of Oligonucleotide and Modified Analogs. Seillac, FRANCE, April.

1994 **The 6th International Conference on Chronopharmacology and Chronotherapeutics**: Chronobiology of Thymidine Kinase and its Application in Cancer Chemotherapy. Amelia Island, FL, July.

GRANT SUPPORT

Current Funding ---- NIH/DoD

1. **NIH/NCI** (N01-CM-47015-45; HHSN261200522007C): Preclinical pharmacological studies of antitumor and other therapeutic agents". **PI: Ruiwen Zhang, M.D., Ph.D.** (25% effort); 12/15/04-12/31/2011 (This award is the competitive renewal application of N01-CM-07111; 12/1/99-12/15/2004). Annual budget: $212,006 (Total budget $1,714,794).

2. **NIH/NCI** (R01 CA 112029): MDM2 as a Negative Regulator of $p21^{waf1/cip1}$. **PI: Ruiwen Zhang, M.D., Ph.D.** (20% effort); 01/01/05-12/31/2009; Annual budget 267,064 (Total budget 1,340,856).

3. **NIH/NCI** (N01CN85183): Randomized, double blind, placebo controlled phase II trial of celecoxib in subjects with actinic keratoses. PI: Craig Elmets, M.D., **Pharmacology PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 9/30/98-10/01/2004.

4. **NIH** (R01 CA 86172): Phthalocyanine PDT: In Vivo Responses and Mechanisms. P.I.: Craig A. Elmets, M.D. **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** (10% effort); 03/01/2000-02/28/2005.

5. **DoD Prostate Cancer Research Program** (W81XWH-04-1-0845): MDM2 as a Target for Prostate Cancer Prevention and Therapy (Post-Doctoral Training Award). Mentor: **Ruiwen Zhang, M.D., Ph.D.**, Post-Doc: Zhang Z, MD, PhD, 09/30/04-10/01/06 (total budget $125,00)

6. **NIH/NCI** (R01 CA104035): A novel inhibitor of Stat3 for prostate cancer therapy. P.I. Jing, Naijie, Ph.D., **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 04/01/2005-03/31/2010. (This funding is anticipated: primary score 178, percentile 3.9).

Current Funding ---- Industry and Other Sources

1. Hybridon, Inc.: Disposition of Oligonucleotides: Pharmacology and Toxicology. **PI: Ruiwen Zhang, M.D., Ph.D.** (30% effort); 08/01/93-07/31/2005 (Annual budget $160,000; total budget $2,040,000.)

2. **NCCN**: A Phase I and Pharmacologic Trial of Sequential Administration of Bi-weekly Gemcitabine as a 24-hour IV infusion followed by Irinotecan as a 24-hour IV Infusion in Adult Cancer Patients. PI: M. Wasif Saif, M.D. **Co-PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 1/28/2003-1/27/2006. (Pharmacology budget $140,000)

3. **Eli Lily and Co.**: Dexamethasone in Lung Cancer. P.I.: John J. Rinehart, M.D., **Co- P.I.: Ruiwen Zhang, M.D., Ph.D.** (15% effort); 03/01/2003-02/28/2007.

Pending Funding:

1. Congressionally Directed Research: Experimental Therapeutics targeting Angiogenesis. **P.I.: Ruiwen Zhang, M.D., Ph.D.** (20% effort); 01/01/2005-12/31/2006

Past Funding

1. NIH/NCI (CA-40530): Mechanism of Toxicity of Fluoropyrimidines. PI: Robert B. Diasio, M.D., **Co-PI: Ruiwen Zhang, M.D., Ph.D.** (20% effort); 7/1/88-6/30/96; $1,055,458.

2. American Cancer Society: Clinical Investigation of Dihydropyrimidine Dehydrogenase in Cancer Patients. PI: Robert B. Diasio, M.D., **Co-PI: Ruiwen Zhang, M.D., Ph.D.** (15% effort); 01/01/94-12/31/95; $150,000.

3. NIH/NCI (CA 62164): Genetic Polymorphism of Dihydropyrimidine Dehydrogenase. PI: Robert B. Diasio, M.D., **Co-PI: Ruiwen Zhang, M.D., Ph.D.** (20% effort); 12/09/93-11/30/97; $942,193.

4. Biocryst, Inc.: Plasma- and Serum-Protein Binding of BCX-34.**PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 10/1/95-9/30/96; $10,000.

5. SmithKline Beecham, Inc.: Phase I/IIa Study of Sequential Ifosfamide and Topotecan in Patients with Small Cell Lung Cancer. PI: Francisco Robert, M.D., **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** 01/01/97-12/31/99; $40,000.

6. Eli Lilly and Co/Lilly Oncology: Phase I/IIa Study of Cisplatin, Dexamathasone and a 24-hour infusion of Gemcitabine in patients with relapsed or Refractory Non-Hodgkin's Lymphoma. PI: Francisco Robert, M.D., **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** 12/01/97-12/31/99; $75,000.

7. Ontario Ministry of Health, Canada: Clinical Study of Time-dependent Therapeutic Effects and/or Toxicity of Zidovudine (AZT) in AIDS Patients. PI: Georg A. Bjarnason, M.D; **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** 12/01/97-12/31/99; $286,600

8. Rhone-Poulenc Rorer: Phase I Dose Escalation Study of Taxotere and Continuous Infusion of Topotecan in Patients with Advanced Malignancies. PI: James A. Posey, M.D., **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.**, 05/01/98-4/30/00; $101, 232

9. IDEC Pharmaceuticals, Inc. (IDEC132-01 Phase I): Phase I Study of 9-Amino-camptothecin in Patients with Solid Tumors (Pharmacology Study). **PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 12/01/97-11/31/2000; $178,046.

10. NIH/NCI (N01 CN65024): A Phase II Trial of Sulindac in Patients with Cervical Intraepithelial Neoplasia (CIN) Grade 3 -Histological Reduction of CIN 3 and Modulation of Surrogate Endpoint Biomarkers.PI: Ronald Alvarez, M.D., **Pharmacology PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort) 09/30/96-9/29/98; $629,074 (Extension to 10/1/2001 with additional support).

11. IDEC Pharmaceuticals, Inc.: Phase II Study of 9-Aminocamptothecin in Patients with Solid Tumors (Pharmacokinetics/ Pharmacodynamics Study). **PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 05/01/98-4/30/2001; $37,870.

12. NIH/NCI (U01CA76607): Therapeutic Studies of Anaplastic Gliomas. PI: Steven Rosenfeld, M.D., **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.**, 04/01/98-3/31/2002; Yearly Costs: $102,923.

13. NIH/NCI: Evaluation of Chemopreventive Agents by in vitro Techniques. (NCI-CN-85093-63). PI: Donald Hill, Ph.D., **Co-PI: Ruiwen Zhang, M.D., Ph.D.**); 7/1/99-6/30/2003. (Master Agreement)

14. NIH/NCI (R01 CA 80698): MDM2 Oncogene as a Target for Modulating Cancer Therapy. **PI: Ruiwen Zhang, M.D., Ph.D.** (30% effort); 04/01/99-3/31/2004; $997,298.

15. NIH: Breast Cancer SPORE. P.I.: K Bland, M.D. (P50 CA89019), **Co-Investigator: Ruiwen Zhang, M.D., Ph.D.** (5% effort); 03/01/2000-02/28/2005.

16. Industrial Sponsor: Pre-clinical Evaluation of Antisense Anti-XIAP Oligonucleotides in PC-3 Model. **PI: Ruiwen Zhang, M.D., Ph.D.** (5% effort). 11/01/2002-10/30/2003.

17. NIH/NCI: Preclinical Pharmacological Studies of Antitumor and Anti-HIV Agents. (N01-CM-07111). **PI: Ruiwen Zhang, M.D., Ph.D.** (15% effort); 12/1/99-12/15/2004.

PATENTS

1. **A method for down-regulating gene expression.** (US Patent No 5, 591,721)

2. **Use of 2'-substituted oligonucleotides to down-regulate gene expression.** (European Patent Serial No. 95938213.6)

3. **MDM2-Specific Antisense Oligonucleotides** (US Patent No. 6,013,786)

4. **Methods of down-regulating gene expression.** (US Patent No. 6,608,035)

5. **Down-regulation of gene expression by colorectal administration of synthetic oligonucleotides.** (US patent filed, No. 08/846, 427, 04/30/97)

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2. Chen Z, **Zhang R**, Qiu J, Pan Z. Effects of occupational lead exposure on workers' health. *Chin J Prevent Med* 1985; 9(4): 216-219.

3. Zhang R-W, Zhu G, Liu Z, Yang Y, Qiu J, Sheng Y, **Zhang R**. Spectrophotometric determination of air lead with tetra-(p-trimethylammoniumphenyl) porphyin. *J Labor Med* 1985; 2(1): 61-63.

4. Zhu G, Zhang R, Yang Y, **Zhang R**, Sheng Y, Qiu J, Liu Z. Spectrophotometric determination of urinary lead with tetra-(p-trimethylammoniumphenyl) porphyin. *J Labor Med* 1985; 2(2): 79-82.

5. Tao X, Sun Y, Wang M, Xue S, **Zhang R**, Jiang X, Wang Y. The investigation of health effects on workers exposed to chlordimeform. *Chin J Ind Hyg Occup Dis* 1985; 3(5): 272-274.

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7. Xue S, **Zhang R**. Overview on sister chromatid exchanges (SCE) as a monitoring index for occupational exposure to chemicals. *J Labor Med* 1985; 2(2): 66-71.

8. **Zhang R**, Xue S, Wang Y. Measurement of pesticide contamination on body surface of sprayers through regional and proportional sampling strategy. *Occup Med* 1986; 13(3): 2-4.

9. Lin W, **Zhang R**, Gu Z, Wang X, Zhang R-W, Jiang X, Xue S, Wang Y. Urinary chlordimeform and its metabolites as a monitoring index for occupational exposure to chlordimeform. *Occup Hlth Railroad* 1986; 1: 14-17.

10. **Zhang R**, Lin W, Wang X, Gu Z, Qiu J, Xue S, Wang Y. Health effects of chlordimeform in exposed sprayers. *Chin J Prevent Med* 1986; 20(3): 186-187.

11. Wang X, **Zhang R**, Gu Z, Lin W, Xue S. Occupational chlordimeform poisoning: Case report. *J Labour Med* 1986; 3(2): 9-11.

12. Chen Z, Fi H, **Zhang R**, Qiu J, Pan Z. The study of zinc protoporphyrin as a screening index for occupational hazards of lead. *Natl Med J China* 1986; 66(8): 484-487.

13. Pan Z, Qiu J, **Zhang R**, Chen Z, Gu J, Xue S, Wang Y. The study of blood lead and free protoporphyrin as screening indices of occupational exposure to lead, an example of application of discriminant analysis. *Chin J Ind Hyg Occup Dis* 1986; 4(3): 144-147.

14. Wang M, Zhou Z, Li H, **Zhang R**, Xue S. Risk assessment of occupational exposure to chlordimeform. *Chin J Ind Hyg Occup Dis* 1987; 5(1): 50-53.

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16. **Zhang R**, Wang Y, Zhang R, Li H, Jiang X. Urinary formic acid in employees exposed to formaldehyde. *Occup Med* 1988; 15(5): 55-57.

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22 Xue S, Wang M, Jiang X, Li F, **Zhang R**, Zhou Z, Gu X. Risk assessment of Occupational exposure to chlordimeform. In: Xue S and Liang Y (eds): *Occupational Health in Industrialization and Modernization*, Shanghai Medical University Press, 1988; pp. 34-36.

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MISCELLANEOUS/Course Developed

Modern Drug Design and Development (PHR725)

Course Director: **Ruiwen Zhang, MD, PhD, DABT**
Credit Hours: **3**
Students: PhD students in Pharmacology, Toxicology, Microbiology, Chemistry, and other life sciences (2nd year and above)
Learning Objectives: Understanding principles and practice of drug discovery, evaluation and development.

Major Lectures:

- Introduction to MDDD
- The Evolving Drug Discovery and Development Process
- Drug Approval Procedure and Regulatory Issues
- Rational Drug Design I: Target Discovery
- Rational Drug Design II: Target Validation
- Rational Drug Design III: Computer-Aided Drug Design
- Rational Drug Design IV: Combinatorial Chemistry and High-Volume Screening
- Rational Drug Design V: Biotechnology
- Rational Drug Design VI: Novel Drug Delivery System
- Rational Drug Design VII: Structure Biology
- Rational Drug Design VIII: Genomics/Proteomics
- Pre-clinical Evaluation of Drugs
- Disease Models
- Pharmacokinetics and Pharmacodynamics
- *In vitro* and *in vivo* Toxicology
- GLP/GMP/GCP
- Clinical Pharmacology in Drug Development
- Pharmacogenetics/Pharmacogenomics
- Clinical Trials
- Contract research
- Intellectual properties protection